51. The method of claim 31, wherein the GAD is synthesized on a peptide synthesizer.

52. The method of claim 31, wherein the GAD is purified from the central nervous system tissue.

53. The method of claim 31, wherein the patient is a prediabetic patient having autoantibodies to GAD.

54. The composition of claim 35, wherein the GAD is GAD65.

55. The composition of claim 35, wherein the GAD is recombinant GAD.

56. The composition of claim 35, wherein the GAD is synthesized on a peptide synthesizer.

57. The composition of claim 35, wherein the GAD is purified from the central nervous system tissue.

Remarks

The paragraph numbering of the office action is used in responding to the Examiner's comments. Support for dosages is provided at p. 21 , second paragraph. Support for synthesis of GAD on a peptide synthesizer is provided at p. 12, 3rd paragraph. Support for recombinant GAD is provided at p. 12, 4th paragraph. Support for purification of GAD from the CNS is provided at p. 9, last paragraph. Support for a prediabetic patient is provided at e.g., p. 6, second paragraph. Unless otherwise indicated claim amendments are for purposes of improved clarity. Claim amendments are made without prejudice and should not be construed as an acquiescence in any ground of rejection.

3-4. A cross-reference to related application has been included as suggested.

5. Copies of references AS, BA, BN and BT are attached. References AN and AZ will follow under separate cover.

7. The title has been changed.

8-9. Trademarks have been designated as suggested by the Examiner.

10. The minor errors in the specification noted by the Examiner have been corrected.

18. Reference to preselected dosages in claim 31 has been deleted.

1. Rejection under 35 USC §112, first paragraph

All of the claims stand rejected on the ground that undue experimentation would be required to practice the invention as claimed. Initially, it is noted that the claimed method is a relatively simply one. The method specifies that an effective dosage of GAD is administered to a patient so as to inhibit development of IDDM. Although it might be agreed that some experimentation might be required to achieve optimize efficacy in some patients or to avoid side effects, this does not mean that the claimed methods lack enablement.

> It is improper for Office personnel to request evidence of safety in the treatment of humans, or regarding the degree of effectiveness.

MPEP §2107.

Rather, it is sufficient that the claimed methods produce a discernable beneficial effect in at least some patient ("a device must be totally incapable of achieving a useful result" *Brooktree Cor. v. Advanced Micro Devices, Inc.* 24 USPQ2d 1401, 1412 (Fed. Cir. 1992). The burden is on the Examiner to show that it is more likely than not that such minimal level of utility could not be achieved, or could only be achieved with undue experimentation. If, when all the facts have been considered,

the evidence is in "equipoise," an inventor is "entitled to a patent." *In re Oetiker*, 24 USPQ2d 1443, 1447 (Fed. Cir. 1992) (Plager, J., concurring). The Examiner's specific comments are now addressed in turn.

The Examiner says that treatment can only be effective if administered before onset of autoimmune disease, and that such onset is not predictable. In response, another aspect of the present application relates to methods of diagnosing IDDM before onset of disease. It has been found that autoantibodies to the pancreatic 64 kD antigen or GAD occur prior to the onset of disease, and GAD provides an analytical reagent for detecting such autoantibodies as described in the specification at p. 6, second paragraph. Thus, the diagnostic methods of the application allow identification of prediabetic patients, and hence therapeutic invention, before irreversible damage has occurred.

The Examiner cites Tisch as teaching that an administered peptide may have an immunogenic as well as tolerogenic effect. The Examiner says the specification provides insufficient guidance for achieving the latter. However, general principles for achieving a tolerogenic response rather than an immunogenic response were within the state of the art at the date of the invention. For example, a standard immunology textbook available at the priority date of the invention indicates that either low or high dosages of antigen favor a tolerogenic response, whereas intermediate dosages favor an immunogenic response (Benjamini & Leskowitz, *Immunology: A Short Course* (Liss, 1988) (at p. 256). This textbook also indicates that absence of adjuvant and use of unaggregated antigen favor a tolerogenic response. Given this guidance, it is submitted that undue experimentation would not be expected to be required to obtain at least some benefit in at least some patients for administration of GAD.

The Examiner says the high degree of specificity required for clonal deletion in diseases such as IDDM having more than one autoantigen. However, it has been reported that a T-cell response to GAD65 develops early in development of IDDM and subsequently spreads to other β-cell antigens in a cascade of responses that ultimately lead to IDDM (see Tian et al., *Nature*

*Medicine* 12, 1348 (1996), column 1, first paragraph). Thus, it would be expected that inducing tolerance to GAD65 would abort subsequent events in the cascade of events leading to IDDM. This expectation is supported by the several publications reporting that GAD65 or peptides thereof inhibit development of IDDM in laboratory animals (see e.g., Tisch et al. (BO), Kaufman (BG), Tian et al., *supra*, Peterson et al., *Diabetes* 44, 1478 (1994), and Pleau et al., *J. Immunol. Immunopath.* 76, 90-95 (1995)).

The Examiner cites Lernmark as teaching that the mechanism of GAD65-induced protection is critical to understanding of autoimmune disease. Although understanding the mechanism by which protection is conferred might provide additional information as to the nature of autoimmune disease, it is not required for enablement of patent claims. The issue in determining enablement is not how the method works, but whether the claimed method would result in at least some benefit in at least some patients.

The Examiner cites Harrison as teaching the administration of GAD risks side effects due to the occurrence of GAD in tissue other than brain. However, Harrison recognizes that GAD is a "strong candidate" for therapeutic use (at p. 724). Moreover, as noted above, it is "improper for Office personnel to request evidence of safety in the treatment of humans."

The Examiner further states that applicants have given no guidance how peptide therapy would overcome autoreactive T cell escape mechanisms in humans. In response, it is submitted that the existence and extent of such mechanisms is purely speculative. The Examiner has not fulfilled the PTO's burden of showing that such mechanisms would more likely than not prevent any beneficial effect in any patient, particularly when they do not in the animal models described in the publications cited above.

For all the reasons, withdrawal of the rejection is respectfully requested.

14. The Examiner makes additional marks with respect to linking GAD to an immunoglobulin as specified in claims 32 and 36. These

claims have been cancelled without prejudice to moot the rejection.

15. The Examiner makes additional remarks with respect to the modified GAD polypeptides referred to in claims 33 and 37. These claims have been cancelled without prejudice to moot the rejection. The Examiner's further remarks concerning GAD fragments have been mooted by claim amendments.

22-23. Claims 31 and 35 stand rejected as anticipated by Atkinson. The Examiner says Atkinson teaches administration of the pancreatic 64 kD protein, which is GAD, to prevent or slow the onset of IDDM. This rejection is respectfully traversed.

For a reference to anticipate the claimed invention, the reference must provide an enabling disclosure. *See, e.g., In re Grice,* 133 USPQ 365 (CCPA 1962). Atkinson does not provide an enabling disclosure because the 64 kDa antigen was not available in sufficient amounts or purity to produce therapeutic compositions or use in therapeutic methods. As noted in the specification (at p. 21), mg quantities of GAD are required to treat a single patient. Comparable dosages, on a weight-for-weight basis, have been reported in later publications reporting induction of tolerance in mice using GAD65. Tisch et al., *Nature* 366, 72 (1993); Kaufman et al., *Nature* 366, 69 (1993) (reporting dosages of 50 μg and 10 μg GAD65 per mouse).

Yet even producing 64 kD antigen from pancreatic cells in sufficient quantity and purity for amino acid sequencing has proved an extremely difficult task. Using the best microsequencing techniques, it has been reported that 5-50 pmol of protein can be sufficient for amino acid sequencing (Hunkapillar et al., *Method Enzymol.* 91, 399-413 (1983)), which for GAD65 is equivalent to about 0.3-3 μg. The difficulty in purifying even μg quantities arises in large part because of the very small percentage (~0.014%) of β-pancreatic cells constituting the 64 kDa antigen. See Baekkeskov et al., *Diabetes* 38, 1133-1141 (1989). Before the present invention, one of the present inventors, Dr. Baekkeskov, spent a year attempting to

purify 64 kD antigen from 26 human islet cell preparations. However, she did not obtain sufficient quantities to obtain even a partial amino acid sequence, even though she collaborated with Drs. Hunkapiller and Hood, who had the best microsequencing facility in the world at the time and had pioneered the microsequencing technique. A declaration from a copending case by Dr. Baekkeskov describing these events is attached.

Given the difficulties in producing even the μg quantities of 64 kD needed for amino acid sequencing from a natural pancreatic source, it follows that producing the mg plus amounts needed for administering to a single patient, much less conducting a clinical trial to demonstrate efficacy and safety would have been an impractical and virtually impossible task that no one would have undertaken. Only after the present inventors' insight that the 64 kDa autoantigen was GAD65, which allowed purification from more abundant sources such as brain or a recombinant cellular expression system, did realization of the claimed therapeutic compositions and methods become feasible.

24-25. Claim 35 stands rejected as allegedly anticipated by Chang. Chang is said to teach the use of GAD in combination with Freund's adjuvant as a pharmaceutical composition. This rejection is respectfully traversed. Freund's adjuvant promotes A strong and prolonged immune response and is typically used in the generation of antibodies to a given antigen in laboratory animals. However, a frequent side effect of administering Freund's adjuvant is the induction of aggressive and persistent granulomas (see Harlow & Lane, *Antibodies: A Laboratory Manual* (CSHL 1988)) at p. 98. For this reason, Freund's adjuvant is never used in humans. Accordingly, Freund's adjuvant is not a pharmaceutically acceptable carrier suitable for human administration, as specified in the amended claims.

28-29. Claims 31, 32, 35 and 36 stand rejected as obvious over Adkinson, in view of Dorf and Huston. Huston is cited as teaching linkage of an antibody to a protein of interest. Dorf is cited as discussing the linkage of antigens to spenic cells to induces tolerance. It is believed that this rejection was

intended to be applied only against claims 32 and 36, because claims 31 and 35 do not refer to linking antigen to immunoglobulins or cells. Claims 32 and 36 have been cancelled without prejudice mooting the rejection.

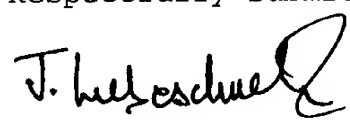
31. Claims 33 and 37 stand rejected as obvious over Atkinosn, in view of Dorf, and Huston, in further view of Wraith. Wraith is cited as discussing analogs of myelin protein that bind with high affinity to the major histocompatiability complex without activating TH cells. Claims 33 and 37 have been cancelled to moot the rejection.

Other Matters

The Examiner's attention is drawn to two other families of patent filings by Atkinson et al. and Tobin et al. cited on the attached supplemental information disclosure statement whose disclosures are directed to similar subject matter to that of the present application. The Examiner is asked to review pending continuations of the cited patents for interference issues.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at (650) 326-2400.

Respectfully submitted,



Joe Liebeschuetz
Reg. No. 37,505

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, Eighth Floor
San Francisco, California 9411-3834
Tel (650) 326-2400
Fax (650) 326-2422

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